1. Title

Good morning everybody - or good afternoon, depending on where you come from. I would like to welcome all of you. My name is Wolfram Windisch. I work as a Consultant Physician and Assistant Professor at the Department of Pneumology at the University Hospital in Freiburg, Germany. The topic I am going to address is “Non-invasive ventilation (NIV) for COPD: from scientific evidence to clinical practice”.
Non-invasive ventilation (NIV) for COPD: from scientific evidence to clinical practice

Topics:

- Pathophysiology and rationale for NIV in COPD patients
- NIV for COPD in ICU medicine
- Successful acute NIV in COPD – and then?

2. Topics

Thereby, I will be presenting three sub-topics on noninvasive ventilation, briefly NIV:
Pathophysiology and rationale for NIV in COPD patients
NIV for COPD in ICU medicine
Successful acute NIV in COPD – and then?
3. The respiratory System - 1

The respiratory system consists of two parts, which can be impaired independently from each other by different pathologies:

1. The lungs, which are responsible for the gas exchange.
2. The respiratory pump which regulates mechanical movements to ventilate to lungs.

Impairments of the lungs lead to hypoxemic respiratory failure. This condition is often accompanied by hypocapnia resulting from an increased demand of ventilation aimed at compensating for hypoxemia. In contrast, impairments of the respiratory pump typically lead to hypercapnia in addition to hypoxemia as a result of hypoventilation.
4. The respiratory System - 2

According to this basic pathophysiology, pulmonary failure (or type 1 respiratory failure) is target for oxygen treatment, but in contrast, artificial mechanical ventilation is inevitably needed to treat ventilatory failure (or type 2 respiratory failure).
5. **Respiratory pump**

The respiratory pump is complex and contains several anatomical structures:
- The central nervous system with the respiratory breathing centre
- The peripheral nervous system
- The motor endplate with the neuromuscular junction
- The inspiratory respiratory muscles
- The rib cage
6. **Respiratory pump - pathophysiology**

The underlying conditions leading to ventilatory failure are heterogeneous according to the complexity of the respiratory pump. There are:

- **Respiratory drive disturbances**
- **Neuromuscular disorders** such as Amyotrophic Lateral Sclerosis, Myasthenia Gravis, Duchenne Muscular Dystrophy, different myopathies.
- **Mechanical disturbances**, most importantly hyperinflation and rib cage deformities.
- **Thoracic instability**
- **Reduced compliance**
- **Increased airway resistance**
7. Load – capacity imbalance 1

Most conditions lead to an imbalance of the load imposed on the inspiratory respiratory muscles and the maximal capacity of these muscles. Thereby, either load is increased or capacity is reduced; or both conditions attribute to this imbalance.
8. Load – capacity imbalance 2
This is the case in COPD patients. Here, there are several reasons responsible for why load is increased and capacity is reduced, and with the next few slides I will be elucidating the complexity of pathophysiology leading to ventilatory failure in COPD patients.
9. Zone of apposition

It is highly important to recognize that the diaphragm is the “heart of the respiratory pump”. Here, for optimal functioning the configuration of the diaphragm is essential: The muscular part of the diaphragm is attached to the ribs thus acting in an up-down-direction. This is called “the zone of apposition”. Thus, the diaphragm is mainly responsible for lifting the lower rib cage.
10. Diaphragm: normal versus COPD

In COPD patients, however, the diaphragm is considerably flattened as a result of hyperinflation. Thus, the diaphragm has lost the ability to lift the lower rib cage. In contrast, in severely hyperinflated COPD patients the diaphragm might even contrarily perform paradoxical movements in case of the diaphragm being horizontally aligned.
Reduced capacity

Diaphragm flattening
• Abnormal geometry
• Muscle shortening

Cellular alterations
• Loss of contractile proteins

Co-morbidities
• Heart failure
• Diabetes mellitus

Following treatment
• Steroids
• VIDD

VIDD = ventilator induced diaphragmatic dysfunction

11. Reduced capacity

There are further reasons for why capacity is reduced: It is well recognized that COPD patients have chronic systemic inflammation, and this supports catabolic processes causing cellular alterations with loss of contractile proteins in the skeletal and also respiratory muscles. Furthermore, co-morbidities often present in COPD patients such as heart failure or diabetes are well known to produce respiratory muscle weakness. Finally, specific treatment interventions such as long-term systemic steroids or ventilator induced diaphragmatic dysfunction in those patients recovering from ICU can also contribute to reduced capacity.
12. Increased load

The reasons for increased load imposed on the respiratory muscles in COPD are also manifold: Hyperinflation and intrinsic PEEP, airway obstruction and the need for increasing inspiratory flow are the main determinants. Thereby, the inspiratory flow is increased due to several reasons:

- Respiratory failure
- Increased respiratory rate
- Reduced inspiratory time because of increased expiratory time that arises from expiratory flow limitation thus allowing sufficient expiration
- Co-morbidities such as anemia or heart failure

Based on these pathophysiological considerations it is conceivable that, in advanced COPD, even minor pathologies producing bronchospasm, increased airway mucus production and airway inflammation such as viral bronchitis are capable of considerably deteriorating respiratory mechanics, thus producing acute respiratory – or to be more specific – acute ventilatory failure.

Then, inspiratory muscle capacity is reduced onwards due to further hyperinflation. In addition, load imposed on the respiratory muscles, and, therefore work of breathing is increased due to the occurrence of an intrinsic PEEP and increased airway resistance. Accordingly, two treatment strategies are essential to overcome this problem:

First, to apply an external PEEP that aims at counterbalancing the internal PEEP and
Second, to administer inspiratory pressure support, thus compensating for respiratory muscle failure.
14. Mechanical Ventilation

This can be achieved by the application of mechanical ventilation. Basically, there are two different forms of how mechanical ventilation can be delivered:

Invasive mechanical ventilation, which requires the placement of artificial endotracheal tubes.

NIV, which refers to the delivery of mechanical ventilation to the lungs using techniques that do not require an endotracheal airway.
15. Major problems

It is of importance to note that most of the problems attributed to mechanical ventilation are related to the access, i.e. the interface, and therefore to the place where the artificial airways of the ventilator meet the biological airways of the living individual. For this reason, invasive and noninvasive ventilation produce considerably different main problems:

Intubation can cause damage of the tracheal mucosa, leads to cough impairments and requires the administration of sedative drugs, which increases the likelihood of acquiring nosocomial pneumonia, and this is clearly known to negatively impact on prognosis.

On the contrary, NIV does not increase the likelihood of acquiring nosocomial pneumonia, which is major advantage, but intolerance or failure of NIV might cause a delay in intubation.
16. NIV: where are we? Complications of invasive mechanical ventilation

In addition, there are several further possible complications related to invasive ventilation. These complications are related to:

- Tube insertion
- Invasive mechanical ventilation
- Tracheostomy in those patients with weaning failure
- Importantly, loss of airway defence mechanisms
- Removal of the endotracheal tube

**Table 1: Complications of invasive mechanical ventilation**

<table>
<thead>
<tr>
<th>Related to tube insertion</th>
<th>Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspiration of gastric contents</td>
<td></td>
</tr>
<tr>
<td>Trauma of teeth, pharynx, oesophagus, larynx, trachea</td>
<td></td>
</tr>
<tr>
<td>Sinusitis (nasotracheal intubation)</td>
<td></td>
</tr>
<tr>
<td>Need for suction</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Related to mechanical ventilation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arrhythmias and hypotension</td>
</tr>
<tr>
<td>Barotrauma</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Related to tracheostomy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haemorrhage</td>
</tr>
<tr>
<td>Trauma of trachea and oesophagus</td>
</tr>
<tr>
<td>False lumen intubation</td>
</tr>
<tr>
<td>Glottal edema and edema</td>
</tr>
<tr>
<td>Tracheomalacia, tracheal ulcers and granulation tissue formation</td>
</tr>
<tr>
<td>Tracheo-oesophageal or tracheocutaneous fistulas</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Caused by loss of airway defence mechanisms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspiration colonisation with Gram-negative bacteria</td>
</tr>
<tr>
<td>Pneumonia</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Occurring after removal of the endotracheal tube</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haemorrhage, sore throat, cough and sputum</td>
</tr>
<tr>
<td>Haemophylia</td>
</tr>
<tr>
<td>Vocal cord dysfunction and laryngeal swelling</td>
</tr>
</tbody>
</table>
Acute respiratory failure in COPD: 

**Rationale for NIV**

**Improving respiratory function and comfort**
- Blood gases
- Dyspnea
- Respiratory rate

**Avoidance of intubation and related complications**
- Ventilator-associated pneumonia (VAP)
- Other infectious complications related to catheter placement
- Tracheostomy and weaning failure

**Improving outcome**
- Length of hospital (ICU) stay
- Mortality

17. **Rationale for NIV**

Based on these considerations there are several issues supporting the rationale for NIV in the acute setting:

First, to improve respiratory function and comfort; this refers to
- Blood gases
- Dyspnea
- Respiratory rate

Second, to avoid intubation and related complications; most importantly
- Ventilator-associated pneumonia
- Other infectious complications related to catheter placement
- Tracheostomy and weaning failure

Third, to improve outcome; most importantly
- Length of hospital and ICU stay
- Mortality
18. Association of NIV with nosocomial infections and survival in critically ill patients - 1

Avoiding infectious complications is one major aim of NIV. Obviously, this does not only refer to nosocomial pneumonia. In this study, conventional, i.e. invasive, mechanical ventilation also resulted in higher rates of urinary tract infections and catheter-related infections when compared to NIV.
19. Association of NIV with nosocomial infections and survival in critically ill patients - 2

Importantly, this clearly impacts on outcome with reduced ICU mortality, length of ICU stay, and duration of mechanical ventilation in case of NIV being used.
Conclusions

NPPV should be the first line intervention in addition to usual medical care to manage respiratory failure secondary to an acute exacerbation of chronic obstructive pulmonary disease in all suitable patients.

NPPV should be tried early in the course of respiratory failure and before severe acidosis, to reduce mortality, avoid endotracheal intubation, and decrease treatment failure.

NPPV = noninvasive positive pressure ventilation

20. COPD meta-analysis - conclusions

Several randomized controlled trials have analyzed the impact of early administration of NIV in acute exacerbation of COPD presenting with respiratory acidosis when added to a standard treatment compared to standard treatment alone. From this meta-analysis summarizing these trials it has been concluded that NIV should be the first line intervention to manage respiratory failure secondary to an acute exacerbation that NIV should be administered early, with best evidence established for pH values ranging between 7.20 and 7.35. and that NIV has been shown to improve ICU outcome.
21. COPD meta-analysis – risk for intubation

Thereby, more or less all studies have shown that the risk for intubation is reduced when NIV is used in addition to standard medical care.
22. COPD meta-analysis – risk for mortality

As a consequence, this results in a reduction of the mortality risk, which is primarily due to a reduction in infectious complications related to intubation and the need for sedation.
23. COPD meta-analysis – number needed to treat

When summarizing this meta-analysis - the number needed to treat is 5 for preventing intubation indicating that 5 patients need to be treated with NIV in order to prevent 1 intubation.

Accordingly, the number needed to treat is 8 for reducing mortality indicating that 8 patients need to be treated with NIV in order to prevent 1 death on the ICU.
24. Brochard study - results

Nevertheless, we need to take a closer look at the studies that have established the evidence for this favorable outcome associated with the application of NIV.

This is the very famous study by Brochard and co-workers. Patients had been randomized to receive either standard treatment or NIV in addition to standard treatment. As a result the addition of NIV resulted in substantially lower rates of intubation (26 compared to 74%), lower rates of complications (16 compared to 48%), lower rates of mortality (9 compared to 29%), and lower duration of hospital stay (23 compared to 35 days).

<table>
<thead>
<tr>
<th></th>
<th>Standard (N = 42)</th>
<th>Standard + NIV (N = 43)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intubation</td>
<td>74 %</td>
<td>26 %</td>
</tr>
<tr>
<td>Complications</td>
<td>48 %</td>
<td>16 %</td>
</tr>
<tr>
<td>Mortality</td>
<td>29 %</td>
<td>9 %</td>
</tr>
<tr>
<td>Hospital stay</td>
<td>35 ± 33 d</td>
<td>23 ± 17 d</td>
</tr>
</tbody>
</table>

25. Brochard study – flow diagram 1

However, 42 patients had been randomized to standard treatment alone and 43 patients had been randomized to additional NIV; thus, 85 patients had been included in the final analysis.
26. Brochard study – flow diagram 2

But: more than doubled patients (190) had not been randomized at all. The reasons for not having been randomized were heterogeneous, but remain unclear for a substantial number of patients.
27. Studies versus real life

Therefore, we always have the problem that - due to predefined inclusion and exclusion criteria - we have highly selected patients in most randomized controlled trials. For this reason, there is the question how the results gained by randomized controlled trials translate to everyday clinical practice. Obviously, patient selection is crucial for the success, and severe co-morbidities or associated conditions like left heart failure or even sepsis might negatively impact on the success rates of NIV.

Despite this consideration I would like to emphasize that there is no reason to doubt on these trials and that there is still clear evidence for the positive impact of NIV on outcome when early applied in COPD patients with acute exacerbation presenting with respiratory acidosis.
28. Contraindications for NIV

Regarding patient selection there are some certain conditions, which likely contribute to failure of NIV or can even cause harm when intubation is delayed as a result of unsuccessful NIV. Therefore, clear contraindications for NIV have been established as follows:

Cardiac or respiratory arrest
Severe encephalopathy
Severe gastrointestinal bleeding
Severe haemodynamic instability
Facial surgery or trauma resulting in insufficient mask fitting
Upper airway obstruction
Inability to protect the airway and a high risk of aspiration
Inability to clear secretions
29. Monitoring

In addition, the success of NIV is also dependent on sufficient monitoring. Here, important parameters for minimum monitoring have been summarized with three different main groups differentiated:

1. The clinical monitoring must include:
   - Sensorium
   - Dyspnea
   - Respiratory rate
   - Respiratory distress
   - Mask comfort
   - Compliance with ventilator setting
   and, of course, vital signs

2. Important physiologic parameters also need to be monitored including
   - Arterial oxygen saturation
   - Arterial blood pressure
   - ECG

3. Finally, ventilator settings need to be controlled for
   - Air leakage
   - Patient-ventilator interaction
   and parameter settings
30. Sedation?

A frequently asked and important question refers to how and if COPD patients receiving acute NIV should be given sedation. Despite the fact that this question is of high clinical importance, no clear results have been elaborated by prospective randomized controlled trials.
31. Survey of sedation - 1

There is one interesting survey looking at practices for sedation therapy, analgesic therapy and the use of hand restrains across European and North American ICUs. When focusing on sedation therapy less than 15% of respondents used sedation in more of 50% of patients receiving acute NIV. In contrast, 60% of respondents used sedation either not at all or in less of 25% patients receiving acute NIV. Thus, most patients receiving acute NIV do not receive sedation.
32. Survey of sedation - 2

However, if sedation is provided, there is no clear recommendation for what specific type of medication should be given, although there are some differences between Europe and North America with Lorazepam most frequently given in North America and Morphine most frequently given in Europe.
### Survey of sedation practices during noninvasive positive-pressure ventilation to treat acute respiratory failure

<table>
<thead>
<tr>
<th></th>
<th>North America</th>
<th>Europe</th>
</tr>
</thead>
<tbody>
<tr>
<td>NPPV in ARF ≥25%</td>
<td>37 %</td>
<td>68 %</td>
</tr>
<tr>
<td>Sedation</td>
<td>41 %</td>
<td>24 %</td>
</tr>
<tr>
<td>Analgesia</td>
<td>48 %</td>
<td>35 %</td>
</tr>
<tr>
<td>Hand restraints</td>
<td>27 %</td>
<td>16 %</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>ICU</th>
<th>non-ICU</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sedation</td>
<td>42 %</td>
<td>24 %</td>
</tr>
<tr>
<td>Analgesia</td>
<td>50 %</td>
<td>34 %</td>
</tr>
<tr>
<td>Hand restraints</td>
<td>27 %</td>
<td>16 %</td>
</tr>
</tbody>
</table>


### 33. Survey of sedation - 3

Interestingly, according to this survey NIV was more often performed in Europe than in North America, and this was associated with less sedation in countries more frequently using NIV, i.e. Europe. Clearly, this is just an association and might not be reliably explaining this context, but it might also possibly indicate that less sedation is required in case of more experience.

Very similarly, sedation is less frequently used in the non-ICU environment indicating that, perhaps, too much sedation is given on the ICU.

Nevertheless, this remains speculative and more data is needed to answer the question how sedation should be performed in patients receiving acute NIV.
34. Invasive and noninvasive mechanical ventilation are non-competitive treatment strategies.

It is important to note that invasive and noninvasive mechanical ventilation are non-competitive but rather complementary treatment strategies. Of course, nobody would argue when intubation and subsequent invasive ventilation is still pronounced the gold standard for those patients with most severe acute respiratory failure, in whom any delay of intubation would considerably increase the risk of dying. However, there is also robust data now to conclude – as pointed out before – that NIV with sufficient monitoring should be applied early in the course of respiratory failure in order to prevent intubation and related complications. Of course, there is an area of overlap, for which it might be very difficult to say how to best treat patients, and this is obviously depending on experience, staff training and further scientific evidence.
Although I have noted that invasive and noninvasive mechanical ventilation are non-competitive treatment strategies, there is one study directly comparing both approaches in patients with severe respiratory acidosis presenting with a mean pH of 7.20, thus necessitating immediate mechanical ventilation. As illustrated in the graph of the right hand side both treatment strategies were capable of improving ventilatory status, but intubation could be avoided in no less than 48% of patients starting on NIV. This underlines the potential of NIV also in those COPD patients with more severe acute respiratory failure.
GCS ≤ 8 (n=95; 69% with COPD)

<table>
<thead>
<tr>
<th>Variable</th>
<th>At Start</th>
<th>After 1 h</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pao₂/Fio₂ ratio</td>
<td>139 ± 43</td>
<td>189 ± 42</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Arterial pH</td>
<td>7.13 ± 0.06</td>
<td>7.22 ± 0.05</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Paco₂, mm Hg</td>
<td>99 ± 18</td>
<td>81 ± 19</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>GCS</td>
<td>6.5 ± 1.7</td>
<td>10.5 ± 2.4</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>RR, breaths/min</td>
<td>27 ± 10</td>
<td>28 ± 6</td>
<td>0.652</td>
</tr>
<tr>
<td>HR, beats/min</td>
<td>109 ± 15</td>
<td>107 ± 14</td>
<td>0.036</td>
</tr>
<tr>
<td>BP, mm Hg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>150 ± 24</td>
<td>153 ± 20</td>
<td>0.262</td>
</tr>
<tr>
<td>Diastolic</td>
<td>72 ± 14</td>
<td>69 ± 12</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

GCS = Glasgow Coma Scale

36. Diaz study

Even more extremely, patients with most severe respiratory acidosis with a mean pH of 7.13 and hypercapnic encephalopathy can benefit from acute NIV both in terms of respiratory and neurological function with an in increase in pH and Glasgow Coma Scale, respectively, already after one hour of treatment.
Similarly, in this study on COPD patients with acute hypercapnic encephalopathy and severe respiratory acidosis the improvement in respiratory function was similar when comparing invasive and noninvasive ventilation. However, the rate of unweaned patients was substantially higher in those patients receiving invasive ventilation. Although NIV can not be regularly recommended in all COPD patients presenting with severe respiratory acidosis - as the success of NIV is clearly dependent on experience, staff training, and co-morbidities - the studies shown here clearly demonstrate the potential of acute NIV even in this severely sick group of patients.
38. Nava study - 1

Another scenario, however, is that intubation has become inevitable in COPD patients in order to manage severe acute respiratory failure, but early extubation with the adjunct of NIV is then striven in view of the fact that the risk of acquiring nosocomial pneumonia is acceptable during the first two days of invasive ventilation, but steadily increases with any further day being intubated.

In this landmark study COPD patients intubated for 48 hours who failed the spontaneous breathing trial and who were, therefore, not ready for extubation were randomized to weaning procedures as provided by invasive ventilation or by extubation despite insufficient spontaneous breathing with subsequently starting NIV. As a result, very interestingly, the rate of unweaned patients was higher in case of invasive ventilation being used.
39. Nava study - 2

In addition, survival rates, the duration of mechanical ventilation, the duration of ICU stay, and the rate of nosocomial pneumonia were clearly in favor of NIV. This study, therefore, strongly supports the hypothesis that NIV is also beneficial in patients with difficulties of weaning from invasive ventilation. It also again demonstrates that invasive and noninvasive ventilation are non-competitive and could even be used in an alternating approach.
40. Ferrer study

Subsequent research has further supported the concept of NIV to be used for assisting difficult to wean patients. Thus, weaning success and prognosis are improved, and the rate of tracheostomy can be considerably reduced.
41. Brochard study – late failure of NIV

There is, however, one important issue I would like to draw your attention to, and this is the problem of late NIV failure. Although this study on acute NIV in exacerbated COPD patients – as shown before - has clearly demonstrated the benefits gained by NIV, there were few patients with deterioration of respiratory failure necessitating intubation and subsequent invasive ventilation despite initial success of NIV, even though most patients requiring intubation got intubated during the first 12 hours.
Incidence and causes of non-invasive mechanical ventilation failure after initial success

Maurizio Moretti, Carmela Cilione, Auro Tampieri, Claudio Fracchia, Alessandro Marchioni, Stefano Nava

**Acute exacerbation of COPD**

<table>
<thead>
<tr>
<th>137</th>
<th>Patients with NIV success*</th>
</tr>
</thead>
<tbody>
<tr>
<td>23%</td>
<td>31 Patients with late NIV-failure after primary NIV-success*</td>
</tr>
</tbody>
</table>

*NIV > 24 Std.

42. Moretti Study - 1

This issue has been systematically studied in this trial, where 23% of exacerbated COPD patients with initial NIV success had subsequent NIV failure.
Incidence and causes of non-invasive mechanical ventilation failure after initial success

Maurizio Moretti, Carmela Cilione, Auro Tampieri, Claudio Fracchia, Alessandro Marchioni, Stefano Nava

Late NIV failure:
- lower pH at admission
- higher complication rates
- ICU-Mortality
  - 92% when NIV was continued
  - 53% when intubation was performed


43. Moretti Study - 2

Unfortunately, there was no possibility to predict when late failure of NIV occurs. In contrast, there was a broad variety with late NIV failure occurring between day 3 and day 13. Late NIV failure was associated with lower pH at admission and higher complication rates. Importantly, prognosis is severely reduced when these patients are maintained on NIV; thus intubation is inevitable except for those patients with a “Do Not Intubate” - order.
44. Chu Study - 1

A final question regarding acute application of NIV in COPD patients is: What is going to happen after discharge following successful application of NIV. The truth is that readmission rates are enormously high, once COPD had been successfully treated for acute respiratory failure in hospital.
And despite initial successful treatment the overall prognosis is massively impaired with one-year survival rates reportedly approaching 50%.

For this reason, it is the question if long-term application of NIV in these subjects can prevent the patient from being hospitalized again for treating acute respiratory failure, thus improving prognosis.
Despite the fact that this question is crucial, there is only one study addressing this issue, and this study has shown that NIV as compared to sham ventilation can reduce the probability of recurrent acute hypercapnic respiratory failure. Clearly, more studies on this topic are needed. But nevertheless, this study indicates that there might be a huge potential for long-term NIV to treat chronic hypercapnic respiratory failure, thereby avoiding acute episodes of acute respiratory failure.
... at present
long-term NIPPV cannot be recommended
for the routine treatment
of patients with chronic respiratory failure
due to COPD ...

NIPPV = noninvasive intermittent positive pressure ventilation

47. GOLD report

Regarding long-term NIV, however, very pessimistically - looking at international
guidelines on COPD diagnosis and treatment, i.e. the GOLD guidelines, it is stated
that:

“At present long-term noninvasive intermittent positive pressure ventilation cannot be
recommended for the routine treatment of patients with chronic respiratory failure due
to COPD”.

updated December 2009 edition of the GOLD Report
48. Simonds study

And this pessimistic attitude towards long-term NIV when used for COPD might be attributed to early observations that long-term survival is much more impaired in COPD patients receiving long-term NIV compared to those with restrictive diseases, in whom nobody would doubt that long-term NIV is highly beneficial.
49. Wijkstra meta-analysis -1

In addition, scientific evidence gained by this meta-analysis suggests that physiological parameters - such as lung function, gas exchange or sleep efficiency - do not improve following the establishment of long-term NIV. In particular, PaCO2 only non-significantly improved by a mean 1.5 mmHg. Thus, long-term NIV in these studies did not measurably augment alveolar ventilation.
## A Meta-analysis of Nocturnal Noninvasive Positive Pressure Ventilation in Patients With Stable COPD*

<table>
<thead>
<tr>
<th></th>
<th><strong>IPAP</strong> (cmH₂O)</th>
<th><strong>EPAP</strong> (cmH₂O)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gay et al.</td>
<td>10</td>
<td>2</td>
</tr>
<tr>
<td>Strumpf et al.</td>
<td>15</td>
<td>2</td>
</tr>
<tr>
<td>Meecham Jones et al.</td>
<td>18</td>
<td>2</td>
</tr>
<tr>
<td>Casanova et al.</td>
<td>12</td>
<td>4</td>
</tr>
</tbody>
</table>

*IPAP = inspiratory positive airway pressure  
EPAP = expiratory positive airway pressure  
Wijkstra PJ. et al. *Chest* 2003; 124:337-343

### 50. Wijkstra meta-analysis -2

Importantly, NIV in the assisted mode with mean inspiratory pressures ranging between 10 and 18 cmH₂O have been used, and this is suggested to be considerably low. So, the question is: does it really make sense to provide COPD patients with this form of long-term NIV?
51. Early long-term studies

Moreover, two previous randomized controlled trials have also assessed the long-term outcome when NIV was added to long-term oxygen treatment compared to long-term oxygen treatment alone. Again, mean inspiratory pressures were low: 12 and 14 cmH2O. As a consequence, the effect of NIV on PaCO2 and therefore on alveolar ventilation was negligible. Predictably - in my view - survival benefits could not be achieved by the addition of NIV.

<table>
<thead>
<tr>
<th>IPAP (cmH2O)</th>
<th>EPAP (cmH2O)</th>
<th>ΔPaCO2 (mmHg)</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Casanaova et al.</td>
<td>12</td>
<td>4</td>
<td>ΔPaCO2: +0.4 NPPV: -LTOT: -0.9</td>
</tr>
<tr>
<td>Clini et al.</td>
<td>14</td>
<td>2</td>
<td>ΔPaCO2: -1.0 NPPV: +0.5 LTOT: +0.5</td>
</tr>
</tbody>
</table>

52. McEvoy study 1

This is the most recent randomized controlled trial looking at the outcome of COPD patients when NIV was added to long-term oxygen treatment compared to long-term oxygen treatment alone. Assisted NIV again with low pressure settings have been used in this trial.

In my view, it is difficult to understand why this type of NIV, which has been proven to be physiologically ineffective, has been chosen again for the purpose of this study. As could have been predicted there was no clear effect on PaCO2.
53. McEvoy study 1

Despite this there was a small but significant survival benefit for those patients receiving long-term NIV. However, adherence to therapy was only 4.5 hours on average indicating that a substantial proportion of patients did not adequately use NIV. Therefore, clear evidence for the use of long-term NIV in this form is still lacking.
If the targeted physiological parameter (PaCO₂) remains unaffected by the specific treatment modality (long-term NPPV)...

If artificial ventilation does not improve alveolar ventilation...

How can we expect an improved outcome?

54. How can we expect an improved outcome?

However, if the targeted physiological parameter, which is PaCO₂, remains unaffected by the specific treatment modality, which is long-term NIV.... or in other words:

If artificial ventilation does not improve alveolar ventilation, how can we expect an improved outcome?
Normocapnia during nPPV in chronic hypercapnic COPD reduces subsequent spontaneous PaCO$_2$


55. Windisch study – Respir Med

In clear contrast, PaCO$_2$ could be dramatically reduced during NIV from 60 to 40 mmHg over a period of 9 days. This, however, was only achievable when using a controlled mode of NIV with highest mean inspiratory pressures as individually tolerated after careful establishment. Here, mean inspiratory pressures averaged 30 mbar. Certainly, this is highly experimental.
Outcome of Patients With Stable COPD Receiving Controlled Noninvasive Positive Pressure Ventilation Aimed at a Maximal Reduction of PaCO₂

NPPV (assPCV)
- mean IPAP 28 ± 6 mbar
- mean bf 21 ± 3 /min

N = 34

<table>
<thead>
<tr>
<th>Variables</th>
<th>Prior to NPPV</th>
<th>2 Months on NPPV</th>
<th>Treatment Effect</th>
<th>95% Confidence Interval</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>pH</td>
<td>7.40 ± 0.03</td>
<td>7.43 ± 0.04</td>
<td>0.03 ± 0.04</td>
<td>0.01 to 0.03</td>
<td>0.00%</td>
</tr>
<tr>
<td>PaCO₂, mm Hg</td>
<td>41.4 ± 7.0</td>
<td>40.4 ± 7.0</td>
<td>-0.9 ± 0.9</td>
<td>-0.9 to 0.8</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>PaO₂, mm Hg</td>
<td>51.7 ± 6.9</td>
<td>57.5 ± 6.9</td>
<td>5.8 ± 2.4</td>
<td>5.8 to 6.4</td>
<td>0.002</td>
</tr>
<tr>
<td>HCO₃⁻, mmol/L</td>
<td>32.3 ± 2.5</td>
<td>32.0 ± 2.1</td>
<td>-0.3 ± 0.3</td>
<td>-0.3 to 0.1</td>
<td>0.69</td>
</tr>
<tr>
<td>TlCO, L</td>
<td>6.9 ± 1.7</td>
<td>7.1 ± 1.8</td>
<td>0.2 ± 1.5</td>
<td>0.1 to 1.6</td>
<td>0.69</td>
</tr>
<tr>
<td>FVC, L</td>
<td>2.25 ± 0.67</td>
<td>2.67 ± 0.75</td>
<td>0.42 ± 0.42</td>
<td>0.3 to 0.5</td>
<td>0.01%</td>
</tr>
<tr>
<td>FEV₁, L</td>
<td>1.03 ± 0.54</td>
<td>1.17 ± 0.80</td>
<td>0.14 ± 0.10</td>
<td>0.1 to 0.2</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>FEV₁/FVC, %</td>
<td>47</td>
<td>49</td>
<td>1</td>
<td>1 to 2</td>
<td>0.64%</td>
</tr>
<tr>
<td>Pao₂, mm Hg</td>
<td>38 ± 15.6</td>
<td>39.4 ± 15.7</td>
<td>-1.5 ± 6.5</td>
<td>-4.0 to 1.7</td>
<td>0.33%</td>
</tr>
</tbody>
</table>

2-year survival: 86%


56. Windisch study - Chest

Nevertheless, in this clinical, real life, observational study intermittent NIV using higher pressures in a controlled mode was well tolerated over years and improved blood gases during spontaneous breathing with an increase in PaO₂ of 6 and with a decrease of PaCO₂ of 7 mmHg. Interestingly, lung function also improved as shown by an increase in FEV₁ of 140 ml.

Finally, survival rates were considerably higher than previously reported in the literature. Certainly, randomized controlled trials are needed to verify these findings and to evaluate the role of this specific technique used for NIV.
57. Windisch study - Int J Med Sci
This technique of NIV has recently been labeled as “high-intensity NIV”, and this is clear contrast to the conventional approach using assisted ventilation and lower inspiratory pressures, which has been labeled as low-intensity NIV”.
Certainly, not every patient does tolerate inspiratory pressures of approximately 30 mbar, and it is also not necessary in every patient. On the other hand, some patients need and also tolerate even higher pressures. Thereby, high-intensity NIV refers to the effort of maximally decreasing elevated PaCO2 values and thereby of maximally improving physiology.
58. Severe Respiratory Insufficiency Questionnaire

Another very important issue is health-related quality of life. For the purpose of most specifically assessing health-related quality of life in patients with chronic respiratory failure and the need for long-term NIV, we have recently developed and validated the multidimensional Severe Respiratory Insufficiency Questionnaire with 7 subscales and 1 summary scale. Details on this questionnaire can be adopted from the homepage of the American Thoracic Society, although this homepage needs updating. In addition, the Severe Respiratory Insufficiency Questionnaire has become an international standard tool as 10 professional translations have become available so far.
In a recent multicentre trial the Severe Respiratory Insufficiency Questionnaire has been used prospectively, thereby assessing short-term (i.e. 1 month) and long-term (i.e. one year) effects of NIV on health-related quality of life. As a result, overall health-related quality of life substantially improved already after 1 month summarizing all patient groups, and these improvements could be maintained during the subsequent year during which NIV has been continued. These improvements were most evident when using the specific questionnaire, i.e. the Severe Respiratory Insufficiency Questionnaire, compared to the generic questionnaire, i.e. the Short Form 36.
Importantly, COPD patients had comparable, and in particular not less, overall health-related quality of life benefits than patients with restrictive thoracic or neuromuscular disorders, again when ventilator settings were adjusted to maximally improve blood gases. Thus, there is no doubt that the specific aspects of health-related quality of life related to the specific treatment intervention improve following the commencement of long-term NIV.
61. Dreher study – 1

Very recently, we have directly compared high-intensity NIV to the conventional approach of NIV, i.e. low-intensity NIV, in a randomized cross-over trial. Here, the two different approaches of the two techniques are displayed. Doubled inspiratory pressures and controlled versus assisted ventilation are the main characteristic differences between the two approaches. As a result volumes as externally measured via pneumotachygraph were higher when using high-intensity NIV.
62. Dreher study – 2

The primary outcome was nocturnal PaCO2. Those patients receiving high-intensity NIV first experienced a substantial drop of PaCO2, but PaCO2 increased again when switching from high- to low-intensity NIV. On the opposite, PaCO2 reduction was only sparse in those patients starting with low-intensity NIV first, but clearly aggravated when switching from low- to high-intensity NIV. Accordingly, the mean treatment effect between the two treatment modalities was 9.2 mmHg in favor of high-intensity NIV.
63. German guidelines - overview

Based on recent research German guidelines on long-term ventilation have been published this year. Although the long version is available in German only, there is also a shortened English version available with the citation provided below.
**64. German guidelines - algorithm**

According to this guideline it has been clearly indicated by this algorithm that long-term NIV should be considered in severe symptomatic in COPD patients. In general, two groups of indication have been elaborated:

Patients with history of acute respiratory failure and respiratory acidosis

Patients with severe chronic hypercapnic respiratory failure and severely reduced health-related quality of life.
The question is not: „Is chronic noninvasive ventilation indicated in patients with COPD?”

The questions are: „What is the best technique of NPPV for COPD and what are best indications?”

65. Question
To conclude for long-term NIV in COPD, it is not the global and undifferentiated question: „Is chronic NIV indicated in patients with COPD?” The more detailed question is rather: „What is the best technique for long-term NIV to treat stable hypercapnic COPD and what are the best indications?”
"Clinical practice, however, involves primarily phronesis (practical wisdom): a customized decision for one particular patient”

66. Tobin statement

Finally, I would like to emphasize that clinical decision making should not always follow the recommendations provided by evidence based medicine. Very nicely, Martin Tobin has recently verbalized by referring to Aristotle that

“Clinical practice, however, involves primarily phronesis (practical wisdom): a customized decision for one particular patient”

My personal experience is that we can help many COPD patients with the application of NIV both in the acute and chronic setting. However, several individual factors always trigger my decision if NIV should be started or not. This also obviously determines if benefits can be expected or not. High quality clinical studies are certainly needed, but this should never close the door to our phronesis.
How far can we go with Non-Invasive Ventilation?

Consider:
- Impact of underlying disease and patient issues
- Severe respir. failure: feasible, but don't delay intubation
- Staff training/expertise
- Benefits/problems of RCTs
- ICU – and then?

"Clinical practice, however, involves primarily phronesis (practical wisdom): a customized decision for one particular patient”

Tobin MJ. et al. Chest 2008; 133:1071-1074

67. Conclusion

So, how far can we go with NIV in COPD patients?

There is strong evidence for NIV to be used in acute exacerbation of COPD presenting with mild to moderate respiratory acidosis. NIV appears to be also beneficial in severe acute respiratory failure, but the success is clearly dependent on staff training and expertise, and intubation should not be delayed in case of NIV failure.

The international world has learned a lot from randomized controlled trials, but we have also learned that we need to translate these findings into our every day real life clinical work.

In addition, we will probably not help our COPD patients very much if we do our very best only when these patients are treated on the ICU, but don’t care for them after discharge from the ICU. Here, we also need to consider if long-term NIV is indicated. If so, NIV should be targeted to maximally decrease PaCO2, and this approach has recently been labeled as high-intensity NIV.

Finally, I would like to remind you that every patient needs to be treated on an individual basis.

Thank you very much for your attention!